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Negativity of delayed induced oscillations in a simple linear DDE

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ABSTRACT

In this work we study oscillations appearing in the simple linear delayed differential equation (DDE) of the form $\dot{x} = A - Bx(t) - Cx(t-\tau)$ with $B < C$ in the case of τ larger than the critical value τ_{cr} for which Hopf bifurcation occurs. We study the Cauchy problem proposed by Bratsun et al. (PNAS 102 (41) (2005)) as a description of some channel of biochemical reactions, that is we assume that $x(t) = 0$ for $t < 0$ and $x(0) = x^0 \geq 0$. We prove that for any $B < C$ and $\tau \geq \tau_{\mathrm{cr}}$ there exists a t in the interval $(0, 4\tau)$ for which x loses positivity. We conclude that the proposed Cauchy problem is not a proper description of biochemical reactions or of other biological and physical quantities.

We also consider another Cauchy problem with constant positive initial data. There exists a large set of initial data for which the solution to such a problem becomes negative. Therefore, this Cauchy problem is not a proper description of biological or physical quantities.

1. Introduction

It is well known (compare e.g. [1] and references therein) that genetic regulatory networks can be modelled well using systems of ordinary differential equations (ODEs) that give good insight into intracellular mechanisms. Unfortunately, most biological processes inside a cell are very complicated and systems of ODEs that would take into account all the variables involved in those processes can be solved only numerically and in many cases their qualitative analysis is almost impossible.

Recently, to reduce the complexity of such regulatory networks or to include the fact that some reactions can take some time, delayed differential equations (DDEs) were introduced in the modelling of the networks, compare [2–4]. More precisely, in [3,4] it is assumed that the complicated pathway of protein transcription and translation can be reduced to one single process that takes some time. It is well known that even the simplest model with delay can yield interesting qualitative results, e.g. periodic oscillations (see e.g. [5] or [6]). Despite the question concerning the biological validity of that type of reduction, there appears the question of the form of the initial data. Most processes occurring in a cell are triggered if there is a demand for their results. Therefore, it seems natural to assume that initial data are expressed as a solution to ODEs describing that part of the pathway in which delayed reaction does not occur. This is equivalent to setting the noncontinuous initial data to the form

$$\mathbf{x}(t) = 0 \quad \text{for } t < 0 \quad \text{and} \quad \mathbf{x}(0) = \mathbf{x}^0 \geq 0 \tag{1}$$

where $\mathbf{x}(t)$ denotes the vector of densities of molecules taking part in reactions and $\mathbf{x}^0$ is the vector of initial densities of molecules present in the system.

In this work we study the deterministic description of the reaction channel proposed in [2] that reads

$$\emptyset \xrightarrow{A} P, \qquad P \xrightarrow{B} \emptyset, \qquad P \overset{C}{\Rightarrow} \emptyset, \tag{2}$$

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where A and B denote the rates (propensities) of non-delayed protein production and degradation, and C represents the rate at which delayed degradation of protein is initiated. Delayed reaction (indicated by the wide arrow) represents the initiation of the degradation machine, which eventually degrades the protein after time τ from the initiation (for more details see [2]). The linear DDE of the form

$$\dot{x} = A - Bx(t) - Cx(t-\tau) \tag{3}$$

was proposed in [2] as the deterministic description of the reaction channel (2). In this work we prove that periodic oscillations that occur for $B < C$ when delay exceeds the critical value $\tau_{\text{cr}} = \frac{\arccos(-B/C)}{\sqrt{C^2-B^2}}$ always lose positivity for the Cauchy problem described by (3), (1). Moreover, we show that there is a large set of other kinds of initial data for which solutions to Eq. (3) lose stability. Therefore, this equation seems not to be a proper description of oscillations appearing in biological, chemical or physical problems.

2. The equation $\dot{x} = A - Bx(t) - Cx(t-\tau)$ as a description of biochemical reactions

In this section we study the solutions to linear DDE (3) with initial data of the form (1). General properties of solutions to Eq. (3) are well known and described in many articles and textbooks; compare e.g. [5–8] and references therein. The main property of solutions for $B < C$ is stability of the steady state $\bar{x} = \frac{A}{B+C}$ for $\tau < \tau_{\text{cr}}$ and the occurrence of Hopf bifurcation at $\tau = \tau_{\text{cr}}$ which leads to the periodic behaviour of solutions for $\tau \geq \tau_{\text{cr}}$. It is also obvious that solutions to this equation can lose positivity (compare [9]). From [9] it can be deduced that the general reasons for losing positivity for solutions to DDEs are negative values of the terms with delay. In such a case, if the values of solution are sufficiently large at $t-\tau$ and sufficiently small at t, then the derivative of the solution can take such negative values that the solution decreases very fast and loses positivity as a consequence. In the problem considered, initial functions have to be biochemically reasonable and cannot behave so badly. However, the interesting issue is whether the amplitude of the oscillations that appear due to Hopf bifurcation can be so large that solutions become negative. We show that this is the case.

We are interested in the case where the positive steady state $\bar{x}$ loses stability and Hopf bifurcation occurs, that is $\tau \geq \tau_{\text{cr}} = \frac{\arccos(-B/C)}{\sqrt{C^2-B^2}}$; compare e.g. [10]. Scaling the space and time variables allow us to reduce the number of parameters from 3 to 1. Therefore, without loss of generality, we study the Cauchy problem

$$\dot{\phi} = 1 - b\phi(t) - \phi(t-\tau), \quad \phi(t) = 0 \text{ for } t < 0 \quad \text{and} \quad \phi(0) = \phi^0 \geq 0 \tag{4}$$

with $b < 1$ and $\tau \geq \tau_{\text{cr}}$. Notice that for $b > 1$ there is no change of stability; compare e.g. [5]. In this section we prove that the solution to this problem loses positivity on the interval $[0, 4\tau]$.

Due to the different forms of solutions, one needs to study two cases: for $b = 0$ and for $b \in (0, 1)$, separately. Therefore, in the work we deal with the following Cauchy problems:

$$\dot{x} = 1 - x(t-\tau), \qquad x(t) = 0 \quad \text{for } t \leq 0, \tag{5}$$

$$\dot{y} = 1 - y(t-\tau), \qquad y(t) = 0 \quad \text{for } t < 0 \text{ and } y(0) = y^0 > 0, \tag{6}$$

$$\dot{z} = 1 - bz(t) - z(t-\tau), \qquad z(t) = 0 \quad \text{for } t \leq 0, \tag{7}$$

$$\dot{w} = 1 - bw(t) - w(t-\tau), \qquad w(t) = 0 \quad \text{for } t < 0 \text{ and } w(0) = w^0 > 0, \tag{8}$$

with $\tau \geq \tau_{cr} = \frac{\pi - \arccos(b)}{\sqrt{1-b^2}} \geq \frac{\pi}{2}$, where $\tau_{\text{cr}} = \frac{\pi}{2}$ is the critical value for $b = 0$.

First, we propose an explicit formula for solutions to all problems (5)–(8).

Lemma 2.1. *The solutions to problems (5)–(8) for $t \in [(n-1)\tau, n\tau)$, $n \geq 1$ are given by the following formulae:*

$$x(t) = \sum_{k=1}^{n} \frac{(-1)^{k+1}}{k!}(t-(k-1)\tau)^k, \tag{9}$$

$$y(t) = x(t) + y^0\dot{x}(t) = \sum_{k=1}^{n} \frac{(-1)^{k+1}}{(k-1)!}(t-(k-1)\tau)^{k-1}\left(\frac{t-(k-1)\tau}{k} + y^0\right), \tag{10}$$

$$z(t) = \frac{1}{b}\sum_{k=0}^{n-1} \frac{(-1)^k}{b^k}\left(1 - \mathrm{e}^{-b(t-k\tau)}\sum_{i=0}^{k} \frac{b^i(t-k\tau)^i}{i!}\right), \tag{11}$$

$$\begin{aligned} w(t) &= z(t) + w^0\dot{z}(t) \\ &= \frac{1}{b}\sum_{k=0}^{n-1} \frac{(-1)^k}{b^k}\left(1 - \mathrm{e}^{-b(t-k\tau)}\left(1 - w^0 b\right) - \mathrm{e}^{-b(t-k\tau)}\sum_{i=1}^{k} \frac{b^i(t-k\tau)^{i-1}}{i!}\left((t-k\tau)(1-w^0 b) + w^0 i\right)\right). \end{aligned} \tag{12}$$

Notice that for $k = 0$ the second term in the formula (12) disappears since $k = 0 < 1$.

Proof. Formulae (9) and (11) can be easily proved using the method of mathematical induction.

Let us consider the dependence $w(t) = z(t) + w^0\dot{z}(t)$, where z is the solution to problem (7). One can see that $w(t) = z(t) + w^0(1 - bz(t) - z(t-\tau))$ and, therefore, $\dot{w}(t) = \dot{z}(t) - bw^0\dot{z}(t) - w^0\dot{z}(t-\tau) = 1 - bw(t) - w(t-\tau)$. Moreover, recalling that in the theory of DDE we consider the right-hand side derivative (compare e.g. [5]), in the interval $[-\tau, 0]$ one has $\dot{z}(t) = 0$ for $t < 0$ and $\dot{z}(0) = 1$. Therefore, $w(t) = 0$ for $t < 0$ and $w(0) = w^0$. Uniqueness of solutions yields that w is the solution to problem (8). The same proof shows that formula (10) defines the solution to problem (6). □

Now, we prove the main result concerning negativity of solutions to all problems considered. Notice that it is sufficient to prove it only for the Cauchy problems with the initial data with zero value at $t = 0$, that is problems (5) and (7). From Lemma 2.1 it can be easily seen that if $\dot{x}(t) = 0$, then $y(t) = x(t)$. Similarly, if $\dot{z}(t) = 0$, then $w(t) = z(t)$. Hence, the solution $y(t)$ to problem (6) (similarly the solution $w(t)$ to problem (8)) crosses the solution $x(t)$ to problem (5) (the solution $z(t)$ to problem (7)) at its extremal points. Therefore, the existence of some time $\bar{t}$ such that $x(\bar{t}) < 0$ (or $z(\bar{t}) < 0$) yields $y(t) = x(t) < 0$ (or $w(t) = z(t) < 0$) at the nearest local minimum of the solution x (z, respectively). This local minimum is achieved either in the interval $(2\tau, 3\tau)$ or in $[3\tau, 4\tau)$. Hence, the solution loses stability either in the first of these intervals or in the second one.

Theorem 2.2. *Assume that $\tau \geq \tau_{\mathrm{cr}} = \frac{\pi - \arccos(b)}{\sqrt{1-b^2}}$, $b \in [0, 1)$. For any $\phi^0 \geq 0$ there exists the point $\bar{t} < 4\tau$ such that the solution $\phi(t)$ to problem (4) is negative at $t = \bar{t}$.*

Proof. We prove the statement of Theorem 2.2 for problems (7) and (8). Recall that due to Lemma 2.1 it is enough to prove this statement for $w^0 = 0$ (compare formulae (11) and (12)), that is for problem (7). Although the forms of solutions for $b = 0$ and $b > 0$ are different, the idea of the proof is exactly the same and, hence, we present only the proof for problem (7). In this proof we use the following notation. By $z_n(t)$ we denote the solution to problem (7) for $t \in [(n-1)t, nt]$. Thus, from Lemma 2.1 we have the explicit formula for $z_n(t)$ for any $n \in \mathbb{N}$,

It is easy to see that z_1 is an increasing function and, therefore, z is increasing on $[0, \tau)$. On the next interval one can calculate

$$z_2'(t) = \mathrm{e}^{-bt}(1 - \mathrm{e}^{b\tau}(t-\tau)) \Longrightarrow t_{\max} = \tau + \mathrm{e}^{-b\tau}.$$

Taking into account the inequality $\tau \geq \frac{\pi}{2}$ one can deduce that $t_{\max} < 2\tau$. This implies that the solution z reaches its maximum on the interval $[\tau, 2\tau)$.

On the interval $[2\tau, 3\tau)$ we can easily calculate the derivative of the solution, that is z_3:

$$z_3'(t) = \frac{1}{2}\mathrm{e}^{-bt}(2 + \mathrm{e}^{2b\tau}(t-2\tau)^2 - 2\mathrm{e}^{b\tau}(t-\tau)).$$

The roots of z_3' read

$$t_1 = 2\tau + \mathrm{e}^{-b\tau} - \sqrt{2\tau\mathrm{e}^{-b\tau} - \mathrm{e}^{-2b\tau}}, \qquad \bar{t} = 2\tau + \mathrm{e}^{-b\tau} + \sqrt{2\tau\mathrm{e}^{-b\tau} - \mathrm{e}^{-2b\tau}}. \tag{13}$$

It could be checked that $t_1 < 2\tau$. The function z_3 reaches its minimum at the point $t = \bar{t}$. Notice that $\bar{t}$ can be greater than 3τ but it is always less then 4τ; that is $\bar{t} \in (2\tau, 4\tau)$.

We divide the rest of the proof into two parts. First, we show that for $\tau = \tau_{\mathrm{cr}}$ we have $z_3(\bar{t}(\tau_{\mathrm{cr}})) < 0$ and that $z(\bar{t}(\tau_{\mathrm{cr}})) \leq z_3(\bar{t}(\tau_{\mathrm{cr}}))$, deducing that $z(\bar{t}(\tau_{\mathrm{cr}})) < 0$. Second, we show that $z(\bar{t}) < 0$ for any $\tau \geq \tau_{\mathrm{cr}}$.

The analytical formula for $z_3(\bar{t}(\tau_{\mathrm{cr}}))$ is so complicated that we do not see any easy way to demonstrate analytically negativity of the expression. However, for any b this expression can be calculated plugging $\tau_{\mathrm{cr}}(b)$ and $\bar{t}(b)$ into the expression for z_3. Thus, we have decided to plot the graph of the function $b \mapsto z_3(\bar{t}(\tau_{\mathrm{cr}}(b)), \tau_{\mathrm{cr}}(b), b)$ to demonstrate that the solution is negative. Drawing the graph of $z_3(\bar{t}(\tau_{\mathrm{cr}}(b)))$ with respect to b we observe that $z_3(\bar{t}(\tau_{\mathrm{cr}}(b))) < 0$ for all $b \in (0, 1)$ (compare Fig. 1).

Now, we prove that $z_4(t) \leq z_3(t)$ for $t \in [3\tau, 4\tau)$. Next we prove that $z_3(\bar{t}) < 0$ for $\bar{t} \in [2\tau, 4\tau)$ and this yields $z(\bar{t}) < 0$. Calculating $z_3(t) - z_4(t)$ we obtain

$$\begin{aligned} z_3(t) - z_4(t) &= \frac{1}{b^4}\left(1 - \mathrm{e}^{-b(t-3\tau)}\left(1 + b(t-3\tau) + \frac{b^2}{2}(t-3\tau)^2 + \frac{b^3}{6}(t-3\tau)^3\right)\right) \\ &= \frac{\mathrm{e}^{-b(t-3\tau)}}{6b^4}\{-(b(t-3\tau))^3 - 3(b(t-3\tau))^2 - 6(b(t-3\tau)) + 6(\mathrm{e}^{b(t-3\tau)} - 1)\}. \end{aligned}$$

Let $r = b(t-3\tau)$. For $t \in [3\tau, 4\tau]$ we have $r \geq 0$. Examining the expression in the curl parenthesis and expanding e^r in its Taylor series, we have

$$-r^3 - 3r^2 - 6r + 6(\mathrm{e}^r - 1) = \sum_{n=4}^{\infty} \frac{r^n}{n!} \geq 0.$$

Thus, $z_4(t) \leq z_3(t)$ for any $t \in [3\tau, 4\tau)$ and this completes the first part of the proof of Theorem 2.2.

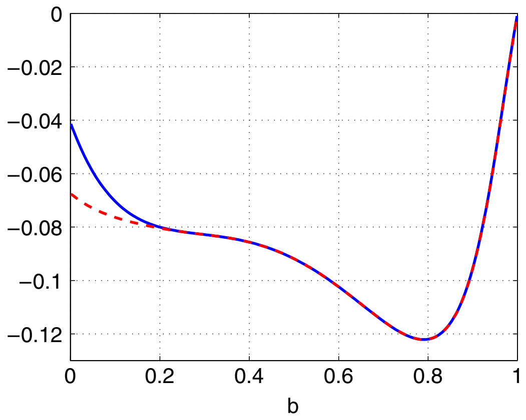

Fig. 1. Graphs of the functions $b \mapsto z_3(\bar{t}(\tau_{cr}(b)), \tau_{cr}(b), b)$ (solid line) and $b \mapsto z(\bar{t}(\tau_{cr}(b)), \tau_{cr}(b), b)$ (dashed line).

Now, we show that $z_3(\bar{t}(\tau))$ is a decreasing function of τ. To avoid confusion we use the explicit formula for the dependence of z_3 on τ:

$$\frac{\mathrm{d}}{\mathrm{d}\tau}(z_3(\bar{t}(\tau),\tau)) = \left(\left.\frac{\partial z_3}{\partial t}\right|_{t=\bar{t}}\right)\cdot\frac{\mathrm{d}\bar{t}}{\mathrm{d}\tau} + \left.\frac{\partial z_3}{\partial \tau}\right|_{t=\bar{t}} = \mathrm{e}^{-b(t-\tau)}(t-\tau-\mathrm{e}^{b\tau}(t-2\tau)^2),$$

since z_3 reaches its minimum with respect to the variable t at the point $t = \bar{t}$ and this yields $\frac{\partial z_3}{\partial t}|_{t=\bar{t}} = 0$. Therefore, after some algebraic manipulations one obtains

$$\frac{\mathrm{d}}{\mathrm{d}\tau}(z_3(\bar{t}(\tau),\tau)) = \mathrm{e}^{-b\bar{t}}(1-\mathrm{e}^{b\tau}(\tau+\sqrt{2\tau\mathrm{e}^{-b\tau}-\mathrm{e}^{-2b\tau}})) < 0.$$

The last inequality can be deduced from the fact that $\tau \geq \tau_{cr} \geq \pi/2 > 1$. This implies that for every $\tau \geq \tau_{cr}$ we have $z_3(\bar{t}) < 0$.

We have already proved that on the interval $[2\tau, 4\tau)$ the inequality $z(t) \leq z_3(t)$ holds. Thus, $z(\bar{t}) < z_3(\bar{t}) < 0$ for every $\tau \geq \tau_{cr}$. □

Remark 2.1. For $b = 0$ and $\tau \approx \tau_{cr} = \frac{\pi}{2}$ we can obtain better approximation of the minimal value of the solution $x(t)$ to problem (5) on the interval $[0, 4\tau]$. Notice that this interval has a length around the basic period of oscillations (compare [11]). On the interval $[\tau, 2\tau)$ the solution $x(t) = t - \frac{1}{2}(t-\tau)^2$ has a maximum at $\tilde{t} = 1+\tau$. Therefore, x has a minimum around $t = \tilde{t} + 2\tau = 1 + 3\tau$, where 2τ is around the half of the basic period. Calculating $x(1+3\tau) = \frac{1}{24}(15+36\tau-36\tau^2+4\tau^3)$ one can see that $x(1+\frac{3\pi}{2}) \approx -0.0739 < x(t_{min}) \approx -0.04$ and the polynomial $x(1+3\tau)$ is the decreasing function of τ for $\tau \in (3-\sqrt{6}, 3+\sqrt{6}) \approx (0.55, 5.45)$.

Problem (4) describes the case where both reactions (instantaneous and delayed) are triggered at $t = 0$. As has been mentioned in the introduction, for the channel (2) we can also consider a slightly more general case, where only the delayed reaction is triggered at $t = 0$. Then for $t < 0$ the problem is described by the simple ODE $\dot{v}(t) = 1 - v(t)$ and we can easily solve it for $v(0) = v^0$. Therefore, the Cauchy problem in this case has the form

$$\dot{v} = 1 - bv(t) - v(t-\tau), \qquad v(t) = \frac{1}{b} + \exp(-b(t-\tau))\left(v^0 - \frac{1}{b}\right) \quad \text{for } t \leq 0 \tag{14}$$

with $b < 1$ and $\tau \geq \tau_{cr}$. However, we see that the solution to problem (14) is just a shift of the solution to problem (4) and, therefore, it becomes negative on the interval $(0, 3\tau)$.

Hence, neither problem (4) nor problem (14) can be used as a description of oscillations of volumes of substances or molecules taking part in biochemical reactions or other biological, chemical and physical quantities.

3. Equation $\dot{x} = A - Bx(t) - Cx(t-\tau)$ as a description of other biological processes

In this section we study the Cauchy problem

$$\dot{u} = 1 - bu(t) - u(t-\tau), \qquad u(t) = \text{const} = u^0 \geq 0 \quad \text{for } t \leq 0. \tag{15}$$

This is a slightly different problem and it cannot be easily considered as a description of biochemical reactions. However, constant initial data are often used in biological applications (compare e.g. [11]) and, therefore, it can be interesting to study also problem (15).

We can easily check that.

Lemma 3.1. *The solution to problem (15) reads*

$$u(t) = u^0 + (1 - (1 + b)u^0)z(t), \tag{16}$$

where $z(t)$ is the solution to problem (7) for $b > 0$ or problem (5) for $b = 0$.

Now, we consider the case $b = 0$. In this case $z(t) = x(t)$. The solution to problem (6) oscillates around its steady state $\bar{x} = 1$ with the amplitude about 2.2. Its minimal value $x_{\min} \approx -0.1$ and its maximal value $x_{\max} \approx 2.1$. Therefore, any solution to problem (15) stays in the interval

$$(u^0 + (1 - u^0)x_{\min}, u^0 + (1 - u^0)x_{\max}) \quad \text{for } u^0 < 1 \quad \text{or} \quad (u^0 + (1 - u^0)x_{\max}, u^0 + (1 - u^0)x_{\min}) \quad \text{for } u^0 > 1.$$

Hence, if $u^0 < \frac{|x_{\min}|}{1+|x_{\min}|}$ or $u^0 > \frac{x_{\max}}{x_{\max}-1}$, then there exists t such that $u(t) < 0$. Otherwise, we suppose that the solution stays non-negative.

Similarly, we can show that for any $b > 0$ there exist a large set of initial data for which the solution to problem (15) loses positivity. Moreover, although positivity or negativity of solutions depends strongly on the shape of the initial function we suspect that positivity is lost in many cases.

4. Summary

In this work we have studied oscillations that appear in the simple DDE model when Hopf bifurcation occurs, that is, for $B < C$ and $\tau \geq \tau_{cr}$, where $\tau_{cr} = \frac{\arccos(-B/C)}{\sqrt{C^2-B^2}}$ for Eq. (3). For the Cauchy problems (5)–(8) describing the biochemical reaction channel (2) from [2] we have proposed explicit formulae for the solutions and shown that any solution to those problems becomes negative on the interval $[0, 4\tau]$. Moreover, for a large class of other kinds of initial data, solutions to Eq. (3) lose positivity on the same interval. This result shows that such simple DDEs cannot be easily used in the modelling of biological or physical phenomena. Models described by systems of DDEs should be built with much more care. The new idea of modelling biochemical reaction channels using DDEs was presented in [12].

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